

CHAPTER IV

INTRODUCTION TO VACCINE THERAPY

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FIRST PRINCIPLES

Let me start quite at the beginning. Long after the principle of prophylactic inoculation had established itself in medicine, it was accepted that to inoculate microbes into the already infected system would be as illogical as to instil further poison into an already poisoned system. Pasteur was the first to teach us here a distinction. He pointed out, in connexion with immunisation against rabies, that a vaccine might legitimately come into application in the incubation period. That was the beginning of therapeutic immunisation; and from that time forth it was recognised that you may legitimately inoculate in the incubation stage, and try to get in in advance of the infection.

But it was in everybody's mind that immunisation took ten days to establish itself. When I showed, in connexion with antityphoid inoculation, that bactericidal substances were very rapidly elaborated, and that the rate of elaboration was influenced by dosage, it became plain that this involved shifting the old landmarks and taking in further territory for therapeutic immunisation.

And one had to put to oneself all sorts of penetrating questions: In connexion with "generalised infections" at what particular stage of the infection one was to regard the body as overmastered by the bacterial poison, and incapable of further immunising response. Again, in connexion with "localised infections," one had to enquire whether

they should not be envisaged as general infections indefinitely arrested in their incubation stage, and whether they might not, in consonance with that, be brought within the sphere of inoculation.

Further consideration suggested that the problem of therapeutic inoculation could be approached also from a point of view different from that taken up by Pasteur. The body had been pictured in the mind's eye as, for the purposes of immunising responses, a single and undivided unit. That is clearly erroneous. One region of the body may be making immunising response while the other is inactive. In the stage of incubation it is presumably only the region which is actually harbouring the microbe, and in the stage of generalised infection, it is presumably the entire body which is incited to respond. Again, in localised infections we may—making here some reserves—assume that we have only localised response.

Placing ourselves at this point of outlook, therapeutic immunisation will, it is clear, be theoretically admissible so long as there remains in the body any part which is not already making its maximum immunising response. And the programme of therapeutic inoculation would accordingly consist in exploiting in the interest of the infected regions of the body the immunising responses of the regions which are uninfected.



BROAD CONTRAST BETWEEN PREVENTIVE AND THERAPEUTIC INOCULATION IN THE MATTER OF THE INTELLECTUAL DEMANDS MADE UPON THE MEDICAL MAN

Preventive inoculation whether it be a question of the now old and venerable process of anti-small-pox vaccination, or of the newer processes of preventive inoculation against cholera, typhoid fever, plague, and pneumonia, makes as good as no intellectual demands upon the Medical Man who carries out the operation. There is not demanded from him any study of the processes of immunisation, or any manipulative skill. In short, we have in preventive inoculation a process which stands perhaps on a par with the switching on of electric light, a process which gives as good results in the hands of the unintelligent and unskilful as in the hands of the skilful and intelligent; in short, a thoroughly democratical, un-intellectual, and a correspondingly popular proceeding. At any rate, no one will ever be tempted to disparage it, or ostracise preventive inoculation as a complicated and intellectually troublesome process.

Therapeutic inoculation stands on a different footing. It makes some intellectual demands. The man who uses it must be able to diagnose the nature of

the bacterial infection he is dealing with, and he should know something about the method by which the body combats bacterial infection, and also he should understand how microbes, in despite of our system of defences, manage to establish themselves and survive in the body. And above all it should be appreciated that the method cannot give its optimum results in the hands of those who make of it a purely empirical procedure and guide themselves only by the clinical results. It will remain true for all time that we cannot make too many or too careful bacteriological examinations, and that the highest level of success can be attained only when we control the effect of our inoculations by frequent measurements of the patient's immunising response. There will also be this to be continuously kept in view in connexion with vaccine therapy, that we are only in our apprenticeship, and that of the broad general principles of the method only some have as yet become clear.

I will now make an attempt to set out those principles in the briefest possible manner.

THE DEFENSIVE MECHANISM OF THE BODY

To combat bacterial infection the organism must have defensive powers. That power of guarding itself against infection we may (the suggestion is Lord Moulton's) call *phylactic power*. The leucocytes and the bacteriotropic substances in the blood fluids we may call *phylactic agents*. But phylactic power in the blood will not be all that is required.

Military similes grow stale; but let me here just point out by the way that the requirements for the defence of a State are not limited to the possession of a standing army. You require also efficient staff work to bring your defensive force to the point attacked. Precisely the same applies to the body.

You must have not only phylactic power in the blood, but also provision for the transport of leucocytes and bacteriotropic blood fluids to the site of infection. This transport of phylactic agents to the site of infection may be called *kata-phylaxis*—the prefix carrying here the same signification as in *cata-plasm* and *kata-phoresis*.

Phylaxis and kata-phylaxis—these are the normal defences of the body. But there are, as you are aware, also resources in reserve. By a process comparable to a mobilisation for the reinforcement of a standing army, the phylactic powers of the blood fluids can be increased. We may call that *epi-phylactic reinforcement*.

ment, or *epi-phylactic response* to inoculation, or simply *epi-phylaxis*.

We now come to something much less familiar—to the conditions which prevail when microbes have established themselves in the tissues. I have in view here conditions to which I first tried to direct attention twenty years ago in connexion with typhoid and Malta fevers—coining for that purpose the terms, "*regions of diminished bacteriotropic pressure*," "*non-bacteriotropic niduses*," and "*non-bacteriotropic envelopes*." These terms may perhaps have been unsuccessfully coined; they have, at any rate, not proved effective missionaries of the idea, and I would propose now to try to put into currency instead the terms *ec-phylaxis*, *ec-phylactic region*, and *ec-phylactic envelope*.

Let me explain the concept of *ec-phylaxis*. For that concept lies, so it seems to me, a little off the track of ordinary medical thinking.

If the reader of this discourse—I am thinking of a reader who has not specially occupied himself with the pathology of infection—were invited to say off-hand in what respect the infected differed from the healthy, he would almost certainly say: that, in his conception, the infected would always have a diminished resisting power to the microbe by which they had been invaded. That doctrine rests upon a misconception of the facts, and it also misses out the most important feature in the picture. In point of fact, the general resistance, *i.e.*, the anti-bacterial power of the blood—is in the ordinary case of infection unaffected; and when affected it is just as often increased as diminished. But the really important point is that there is in every case, without exception, a very noteworthy alteration of defensive power at the seat of infection. The microbes which are culturing themselves here will—and that accounts for their having survived—have abolished or greatly reduced the antibacterial power of the surrounding medium, and they will also, in many cases, have rendered their environment unwholesome country for leucocytes. So in reality the shortcoming in the defences of the infected man lies in this: that there exists within

his system of defences, within his ringed fence, a non-bacteriotropic and unpatrolled or *ec-phylactic region* in which the microbes can grow unrestrained.

It will be convenient for all that is to follow to embody these findings in a chart. For the chart here in view—it is to be a chart of the antibacterial defences of the infected patient—four different signs will be required: the plus sign (+) to signify antibacterial power equivalent to that of the normal man; the double plus sign (++) to signify resisting power increased by epiphyllactic response; the minus sign (−) to signify antibacterial power less than that of a normal man; and the double minus sign (−−) to signify abolished or greatly reduced resisting power. In such a chart the blood of the infected patient will most commonly carry the plus sign; less commonly it would carry the double plus, or the minus sign. The focus of infection will—and this is the most important feature in the chart—invariably carry either a minus or a double minus sign; and in any case, so long as microbes are growing in the nidus of infection, it will carry a lower sign than the circulating blood.

A chart constructed upon these principles would serve as a vade mecum for treatment. It would point out clearly the objects to be attained, and would warn us of the futility of certain schemes of attack. It would indicate what obstacles will always be encountered; and in what directions we may hope to make advances. Again our chart, as I now propose to call it, will suggest a useful classification of therapeutic methods.

Let me point out to you the fundamental lessons it teaches. It teaches us that all effective methods of combating bacterial infection (other than chemotherapy and the surgical extirpation of the microbes) can be ranged under one or two headings. They are either *kata-phylactic procedures*, *i.e.*, procedures which convert the region of negative sign in which the microbes are growing into a region of positive sign; or, they are *epiphyllactic*, that is, immunising,

procedures which convert the minus, or as the case may be, simple plus sign of the blood into a double plus.

The natural order will be to study first the various kataphylactic procedures.

KATAPHYLACTIC PROCEDURES

Evacuation by Incision or Aspiration.

—The rationale of cutting into, or aspirating the focus of infection is that by this we furnish vent to a fluid and white corpuscles whose strength is spent, and bring about the replacement of these by an antibacterial exudate and fresh leucocytes. It would thus, at first showing, seem as if we had in incision and aspiration an ideal procedure for converting a region of negative into one of positive sign. But in reality the method leaves much to be desired. In the case where a phlegmon or an infiltrated tissue is incised, vent is provided only for so much of the exuded fluid as is standing under hydrostatic pressure in the lymph spaces which are laid open and those immediately adjoining; and when this engorgement is relieved the lymph coagulates on the wound and the outflow stanches. In the case where an abscess is incised, the spent products of inflammation are more fully evacuated, but a residue of the exudate remains behind in the infiltrated walls and the recesses of the sac. These considerations and also the lessons of clinical experience make it clear that if we want to convert a region of negative into a region of positive sign, so as to cope satisfactorily with an infection, we shall need to supplement incision or aspiration by other kataphylactic measures.

Further Methods of Evacuation, which may come into Application when the Focus of Infection Has Been Laid Open.—In the special case of a suppurating joint, the only really efficient evacuation and clinically successful treatment is, as Wilhems showed in the War, to lay open the joint and proceed immediately to active movements. Direct mechanical pressure is universally applied for the evacuation of small collections of pus. Washing and syringing come into routine application in open wounds.

The best that these procedures achieve is what the surgeon calls *drainage*, i.e., the emptying out of corrupted fluids from an abscess sac or wound cavity. For drainage in the real scientific sense—i.e., for the emptying out of corrupted discharges not only from the sac but also from the surrounding tissues—further procedures are called for. We have here our choice of two methods.

The one—the procedure of Klapp—is to employ a cupping apparatus upon the wound. One begins by expecting great things from this procedure but one gets very disappointing results. And then it occurs to one that in cupping operations, conducted upon an infiltrated wound, one is up against the very same obstacles as in the laboratory in drawing a coagulable fluid through a filter. The fluid, if it has not already done so before operations commence, clots in the filter and refuses to come through. And if we try to counter that, by putting on increased negative pressure we tear the fabric of the filter.

Dressings with 2.5 to 5 per cent. salt and $\frac{1}{2}$ per cent. citrate of soda furnish a much gentler and more efficacious method of evacuating spent discharges from the tissues around the wound. It can quite easily be shown in the laboratory that serum and other albuminous fluids of low salt content are very rapidly sucked into strong salt solutions.

Procedures for Bringing Active Leucocytes and Antibacterial Serum or Both into the Evacuated or Unevacuated Ecphyllactic Focus.—Of the procedures which may be employed for these purposes, the most important are the employment of hot fomentations, the compression of the superficial veins by Bier's bandages, massage, passive and active muscular movements and the application of appropriate chemical stim-

ulants. Hot fomentations will bring antibacterial serum to the seat of infection; it is perhaps doubtful whether they will bring out leucocytes. Bier's bandages will, by blocking the flow in the veins, and so raising the pressure in the capillaries, produce increased transudation. Massage applied distally to the seat of infection will drive fluid which has exuded into healthy tissues through the ecephylactic focus. Passive and active muscular movements will do the same. And the application of appropriate chemical stimulants to a cut or a granulating surface will call forth an exudation of serum or an emigration of leucocytes, or both.

Spontaneous Kataphylaxis.—It would be unjustifiable to assume that active kataphylactic measures will be requisite in every case. There are occasions when we must resort to these, and again others when we may trust to spontaneous kataphylaxis. In other words, there are occasions when spontaneous emigration of white corpuscles, and normal transudation, and the natural movement of the lymph, will do all the kataphylactic work which is required. The factors which will determine our election between artificial and spontaneous kataphylaxis will be the larger or smaller dimensions of the ecephylactic focus, and the extent to which effective contact between the blood and the fluid in the focus is maintained. When a focus has attained considerable dimensions, and when effective contact with the blood has

been interrupted by massive effusion, or, as in abscess formation, by tryptic excavation of the tissues, spontaneous kataphylaxis will accomplish nothing. A concentrated population of microbes will maintain around itself ecephylactic conditions by quenching the antibacterial power of any instreaming lymph, by paralysing leucocytic emigration, and breaking down pus cells and setting free trypsin. It will also produce auto-inoculations by sending out toxins into the blood and surrounding lymph. And, as the infective focus gathers bulk, it will more and more emancipate itself from the antibacterial influence of the blood, and will *pari passu* with that bring the body generally more and more under the influence of its toxic metabolic products. In such a case, resort to evacuation and active kataphylaxis will of course be imperative. Where we are dealing with foci of comparatively small dimensions, in which effective contact with the blood is still maintained, spontaneous kataphylaxis will often suffice. But even when we have come down to quite microscopic foci, active kataphylactic procedures will, when they can be brought to bear, still bring advantage.

With this I have said all that it will be necessary to say here on the subject of kataphylactic procedures and the combating of ecephylactic conditions. And we may now pass to the discussion of vaccine therapy proper—in other words to the discussion of epiphyllaxis as a therapeutic measure.

VACCINE THERAPY OR EPITHYLLAXIS AS A THERAPEUTIC MEASURE

It will, of course, be necessary to confine ourselves here to a bare general survey. That survey may perhaps with advantage take the form of pointing out the nature of the scientific presumptions which entitle us to expect useful results from vaccine therapy. We may specify three. Among these there are two with which we have already made acquaintance.

(1) It was explained at the very outset that vaccine therapy is, as a matter of actual history, the offspring of pre-

ventive inoculation. We saw that immunisation, undertaken before exposure to infection, suggested the idea of immunisation in the incubation period, and that this in its turn suggested the idea of immunisation in the presence of infection. Now that amounts to nothing more than saying that the fact that immunisation, before exposure was effective, gave ground for hope that immunisation in the incubation stage would succeed, and that in like manner, the fact that immunisation in the incu-

bation stage was effective, inspired the hope that immunisation in the presence of infection would also do good. Before this could be accepted as a valid presumption it was necessary—and that has already been done in the foregoing—to show that these three forms of inoculation are in reality only variants of the same procedure, and there is in reality between them no fundamental difference of principle.

(2) A second presumption which will, to the man who has direct acquaintance with the protective machinery of the body, carry great weight is furnished by the facts which have been embodied in the chart sketched above. No one, so far as I can see, could rise from the perusal of that chart, unconvinced that all our kataphylactic procedures would be rendered infinitely more effective if we had at our disposal instead of a blood carrying a minus or a simple plus sign, a blood which carried a double plus sign. There is thus again here a priori justification for expecting good from vaccine therapy.

(3) We can also obtain from the study of auto-inoculation and its effects warranty for recourse to, and favourable auspices for, vaccine therapy. By *auto-inoculation* is understood, as the reader will be aware, a conveyance of bacterial products from a focus of infection into the blood stream. When a focus of infection has gathered bulk so as to send, even when the body is at complete rest, sufficient toxin into the blood to produce immunising response, with or without constitutional disturbance, we speak of "spontaneous auto-inoculation."

Where active or passive movements, or coughing, or the application of a Bier's bandage, or hot fomentations, or any other procedure conveys toxin-laden lymph into the blood, we speak of an "artificial auto-inoculation." In either case, dosage will determine the event. Where an excessive dose of bacterial products is carried into the blood stream, there will be pyrexial disturbance; the antibacterial power of the blood may be seriously reduced, and not only temporarily, and the patient's condition may be seriously aggravated. Where a smaller dose of bacterial

products is carried in, the antibacterial power of the blood may be increased either directly, or in sequel to a short negative phase, and the patient's condition will improve. There are well attested but exceptional cases, in which such an auto-inoculation has put a definite end to a long persisting chronic infection. But in most cases the improvement is only temporary, and the positive phase over, the infection follows its usual course.

It will be patent to anyone who gives due thought to the matter, that each and all of these results must be reproducible by the agency of vaccines. And from that it is obvious, that if the clinical effects of auto-inoculations had been duly pondered upon, the therapeutic employment of vaccines would have suggested itself, and the doctrine of the negative and positive phase, and the necessity of great caution in dealing with a heavy infection, would have been discovered in connexion with clinical events, instead of in connexion with preventive inoculation against typhoid fever.

Enough and more than enough has now been said to make clear that all sorts of different lines of research, from different points of departure, converge in vaccine therapy, and that we have affair here with a method which reposes upon one of the most fundamental biological generalisations—the generalisation that the animal organism will, in response to the appropriate stimulus (and we do not yet sufficiently know what that means), elaborate protective substances and perhaps, also, put itself otherwise in a better state of defence.

Let us try to see the significance of the fact that vaccine therapy is based upon a firmly established scientific principle. We have in medicine to-day two different categories of therapeutic agents. Those of the one category rest on no scientific foundation—that is to say, we have no grounds other than such as may be afforded by the clinical results, to expect from them any therapeutic efficacy. Of such sort are all the quack remedies; and who shall say how much of the ordinary repertory of medicine would fall into that category? To

the intelligent, it is as gall and worm-wood to have recourse to any of this class of remedies. For when the reputed remedy fails in our hands we never know, unless the clinical evidence in favour is overwhelming, whether there is in the method any shred of utility which it would be worth while to try to extricate.

The other category of therapeutic measures consists of those which rest upon a definite scientific basis. We have examples of such, as I hope, in vaccine therapy; and we have at any rate a definitely accredited example in Ehrlich's *chemotherapy*, or as I should have wished to persuade him to call it, *pharmako-therapy*. The essential feature of all scientifically accredited therapeutic measures is that we, knowing that they must give results, are prepared to devote infinite labour to finding out and eliminating the various causes of failure.

In connexion with this newcomer, vaccine therapy, only one further issue need here engage our attention. It will be proper to consider whether vaccine treatment can or cannot enter into a working alliance with the customary methods of treating bacterial disease. Of these the following are those which must be taken into account: (1) *Treatment by active kataphylactic procedures*; (2) *treatment by antiseptics*; and (3) *treatment by excision or amputation of the focus of infection*. And to these we may perhaps add (4) *the recipe of leaving to unguided nature the task of coping with the infection*.

A few words may be said about each procedure.

(1) Treatment by Active Kataphylactic Procedures.—The relations of vaccine therapy to active kataphylactic measures have already been elucidated. We have seen that kataphylaxis is the complement of epiphyllaxis, and epiphyllaxis the complement of kataphylaxis; and that we must, for the thorough and rapid extinction of an infection, have a working alliance between the two. Let me supplement that by emphasising that when we attribute a cure to kataphylactic measures alone, or to epiphy-

llaxis alone, we are leaving out of sight important elements. Where a cure is attributed to active kataphylactic measures we leave out of sight that in the successful cases the blood may, by nature, have had a high antibacterial power; or again, it may have arrived at this by immunising response to auto-inoculations. Similarly, when cures are attributed to the operation of a vaccine, we forget to take note that cures can be wrought by vaccine therapy only in that special class of cases where spontaneous kataphylaxis fulfils all requirements. And again, when we register cures in these cases we take no cognisance of the time factor, and leave out of account, that with a combination of effective kataphylaxis and effective epiphyllaxis, time can be saved. With this enough has been said to make good that vaccine therapy cannot afford to dispense with active kataphylaxis, nor this latter to hold off from an alliance with vaccine therapy.

(2) Treatment by Antiseptics.—When we set ourselves to explore the theoretical foundations of the therapeutic employment of antiseptics we, at the end, arrive at this, that the advocates of antiseptic treatment do not believe that the body can successfully combat a bacterial infection, but firmly that antiseptics can do so.

The former of these tenets—the tenet that the body is incapable of successfully combating bacterial infection (or at any rate one in a wound)—has since the days of Lister been popularly accounted almost an article of religious belief. As such it is wont to be defended against assault by appeals directed to the emotions. We are bidden to reflect that we have in the doctrine of the defencelessness of the body the mother idea which bestowed upon mankind the gift of antiseptic and aseptic surgery. And we are warned that, if ever this belief should crumble away, inevitably all those antibacterial precautions which have contributed so much to the safety of surgical operations, would be cast to the winds.

And yet, in face of all that, the doctrine of the defencelessness of the body

—is false doctrine. It has, with regard to every species of microbe that has been subjected to the test in the laboratory, been demonstrated that it can be killed by the defensive agents of the body, either by the serum working separately or by the leucocytes. And not only is laboratory proof available, but there is, if we want that, also clinical proof. It is notorious that it has in the war been demonstrated on tens of thousands of cases that bacterial infection of wounds can be successfully combated by resecting the devitalised tissues and then simply suturing.

The importance of these proofs of the antibacterial powers of the body is clear. They cut away the ground from under the feet of all those who find in the presumed defenceless condition of the body, ground for resort to antiseptics and inducement to believe in their efficacy. A priori arguments of every kind are, however, here quite out of place. And no reasonable man will dispute that the issue as to whether antiseptics are effective bactericidal agents, when employed in the body, is purely and simply a matter to be decided by experiment. Further, it will be clear that the issue can be settled only by taking infected wounds, treating them with antiseptics and observing the conditions before and after.

At this point, however, sharp differences of opinion emerge between the laboratory investigator and the clinician. The former holds that the question of the bactericidal potency of antiseptics as applied in wounds can be adjudicated upon only by microscopic examinations and resort to cultures. The clinician for his part insists that the matter is one for his personal arbitrament, and that the bactericidal potency of an antiseptic will be known by the visible effect upon the wound. In point of fact, as always in such cases, both parties will be found to have undertaken their own experiments, employing their own methods.

The bacteriological methods have given in essential almost quite uniform results. Of all the antiseptics that have been tried, there is not one which will keep down the pullulation of microbes

in an unwholesome wound; or extinguish that much sparser bacterial population which is found in a "clean" wound.

The results of clinical observation are in broad agreement with these findings. It would, I think, be universally admitted that antiseptics applied in the conventional manner, *i.e.*, by syringing out the wound once or twice a day, do little or nothing to improve an unwholesome wound, and will not arrest a suppurative process.

But over against this there is evidence of strikingly beneficial results obtained in the War by Dakin's fluid, applied according to the system of Carrel. There is no shutting our eyes to the fact that this conflict of evidences places Medical Science in a fix. There must perforce be error somewhere.

We may assume, for numerous and competent witnesses on each side depose to the findings, that the error is not in the facts. It must consequently lie in the inferences. Now that really tells us with whom the fallacy lies. It cannot lie with the bacteriologist for the very simple reason that he makes here no sort of inference. Consideration shows that his assertion that antiseptics applied in the body are inefficient is merely the assertion that the microbes of the wound are as numerous after as before antiseptic treatment recast and put into another form of words. The clinician, on the contrary, here has recourse to the method of inference, and so exposes himself to fallacy. And in point of fact fallacy lurks in the argument that amelioration in the condition of the wound gives warranty for concluding that the antiseptic applied is in the body an effective bactericidal agent.

To the clinician the whole of this reasoning, working up to the point that he is in error, will naturally enough be quite unconvincing. He will claim that if he is alleged to be wrong, the exact nature of his error should be brought home to his understanding.

That, as a matter of fact, is the sort of claim that no one is entitled to make. But the point will here be waived, and an endeavour may be made to show the

exact nature of the fallacy which is made in assuming that an antiseptic must always act in the capacity of a direct bactericidal agent, and the reader will be trusted to do his best to bring to the discussion of this issue a mind free from prepossessions.

The first point to appreciate is that what actually comes under clinical observation when a wound is treated by the method of Carrel is that the wound is gradually (let us say in the course of a week or ten days of reiterated washings) converted from an unwholesome into a wholesome wound with healthy granulations.

It will be pertinent here to remember in connexion with unwholesome and wholesome wounds that I have shown that the wounds which the clinician classes as *unwholesome*, or *foul*, are wounds with tryptic discharges which favour the growth of every description of microbe; and that the wounds which the clinician classes as *clean*, or *healthy*, are all wounds with an anti-tryptic exudation which completely inhibits the growth of all but one or two species of microbes, and at the same time favours phagocytosis.

It will be seen from this that the clinician does justifiably contend that he can by inspection of the wound discern that Carrel's treatment leads to a striking reduction in the population of microbes.

The point at issue is, however, not that. It is whether the clinician is justified in drawing the inference that the change seen in the wound is attributable to the antiseptic powers of Dakin's fluid.

Consideration will show that that conclusion would be coercive only if it could be established: (a) that treatment by an antiseptic can convert a foul into a healthy wound, and that kataphylactic treatment would be incompetent to do this; (b) that Dakin's fluid can be regarded as simply and solely an antiseptic fluid, and that applied as it is in the method of Carrel it does not exert any kataphylactic action; (c) that the antiseptic power of Dakin's fluid will satisfactorily account for the diminution in the bacterial population of the wound, *i.e.*, for the gradual de-

cline of that population to a certain minimum, and for the fact that exactly the same species of microbes survive in the Carrel wound as in every other healthy wound.

It will be obvious that the *first* of these three theorems cannot be sustained. I have shown that the very foulest wounds can, by treatment with hypertonic salt solution, be in the course of a very few days, transformed into clean, healthy wounds.

The *second* theorem also is untenable. Fleming¹ has shown that Dakin's fluid when introduced into the wound causes a copious exudation of serum. It will therefore act, not simply and solely as a bactericidal agent, but also as a kataphylactic agent. And seeing that the Dakin's fluid is constantly renewed, it will exert a practically continuous kataphylactic effect.

Finally, coming to the question as to whether Dakin's fluid would, by its bactericidal power, be capable of producing the striking change which Carrel's treatment produces in the bacterial population of the wound, that idea also may be dismissed. If Dakin had discovered an antiseptic which was really effective in the wound, *i.e.*, an antiseptic which was not quenched by contact with any kind of albuminous substance, and was endowed with penetrating power, in that case one (or making handsome allowance for accidents) two or three applications would have effectively sterilised the wound. But in wounds treated with Carrel's system, that consummation is not reached, even after hundreds of applications. Again, if Dakin's fluid had really provided an effective antiseptic for use in wounds, sterilisation would have been achieved quite irrespectively of the wound being in an wholesome or unwholesome condition; and it would almost certainly have been accomplished in fewer minutes than it now takes days to, shall we say, semi-sterilise the wound.

Lastly, if Carrel had had at his disposal in Dakin's fluid a really effective

¹ Fleming, Alexander: The Action of Chemical and Physiological Antiseptics in a Septic Wound, Brit. M. J. 7:99, 1919.

bactericidal agent, he could quite easily, by keeping to the old beaten track, have accomplished all that he was set on achieving. He would not to get his good results have needed to evolve his system of constantly repeated irrigation. With this enough has been said to show that the results of the Carrel method should almost certainly be accredited not to antiseptic but to kataphylactic treatment. If this is so it will be clear that the mainstay of antiseptic treatment has given way, and that method is now left without clinical support. The conclusion which follows from all this is that, as things now are, the immunologist will not wish to enter into alliance with antiseptic treatment except in so far as this is, like Carrel's treatment, and perhaps Lister's treatment with undiluted carbolic acid, kataphylactic treatment in disguise.

(3) Treatment by the Extirpation or Amputation of the Focus of Infection.

—The doctrine of the defencelessness of the body which was under consideration in the preceding section had twin progeny. Antiseptic treatment of localised bacterial infection is one of that progeny. Treatment by extirpation of the focus of infection is the other. The surgeon of the Listerian period probably communed with himself somewhat as follows: The body is defenceless against bacterial attack. When there is a surface infection or a focus which communicates with the exterior I must, therefore, apply antiseptics. When, however, the infection is remote from the surface and antiseptics inapplicable, I must plainly hasten to cut down upon and extirpate the focus. And I must do my work so thoroughly that not a single microbe will be left behind in the body.

From this school of thought have proceeded numberless curettings, resections, excisions, and radical extirpations—operations which, while they have often done good, have much more often brought reproach upon surgery, and in particular upon the surgical treatment of tubercular infection.

What now must be the attitude of

the immunologist to the treatment of infections by this method. Plainly there can be no alliance between vaccine therapy and treatment by extirpation until the doctrine of the defencelessness of the body—that doctrine which has up to the present dictated and directed all extirpation treatment—has been abandoned, and until there has been installed in its place the doctrine that bacterial infection can be best combated by organising and marshalling the natural defences of the body. The further terms of alliance would have to be formulated somewhat as follows: (1) Extirpation, when resorted to, should generally be preceded, and should wherever there is a possibility of its being incomplete be followed, by immunising procedures; (2) Extirpation should be resorted to under two sets of circumstances: *firstly*, where the blood fluids and leucocytes cannot, even when assisted by active kataphylactic measures, find access to the focus of infection; and, *secondly*, where immunisation is impeded by auto-inoculations—in other words, where the body is carrying an impossibly heavy load of infection.

(4) A final word may be said upon the recipe of leaving the task of combating bacterial disease to unguided Nature. Vaccine therapy aspires to replacing all ineffective methods of treating bacterial disease by well considered measures of immunisation, and it aspires also (and it is this that concerns us here) to undertaking the treatment of those grave cases of bacterial infection for which we as yet do nothing except leave them to Nature.

It will show how the case stands with regard to these, and at the same time furnish an appropriate ending to this preface, if we here make a rapid survey over the whole territory of bacterial disease, and see exactly how much has been reconnoitred or taken into occupation for vaccine therapy. For this purpose we may divide up that territory into three provinces or subdivisions.

(1) In the first would be ranged all localised diseases of known bacterial origin. This province of disease has during the course of the last eighteen

years been fairly thoroughly explored by trial inoculations of every sort of local infection, followed up by clinical observations and concurrent measurements of the opsonic power of the blood. And in this class of infection, notwithstanding important lacunæ in our knowledge and uncertainty with respect to some of our theoretical foundations, very successful results are obtained. This territory may be regarded as territory provisionally surveyed and taken in for vaccine therapy.

My fellow worker, Dr. Alexander Fleming, has, in the treatise to which this serves as a preamble, furnished a quite admirable precis of the definitely practical outcome of what has in the course of the last fifteen years been learned in the laboratories and out- and in-patient clinics of the Department for Vaccine Therapy in St. Mary's Hospital.

(2) The second province of bacterial disease would be that of septicæmic infection. In this, despite much expenditure of effort, relatively little has been achieved. That is due to the complexities of the problem, and in particular to those introduced by spontaneous auto-inoculations, and also, in part, to the fact that in those septicæmias which are in general hospitals most accessible, technical difficulties in connexion with the opsonic measurements render the construction of immunisation curves nearly impracticable. To put it in brief:—the scientific survey of septicæmic disease has not yet been effectually taken in hand. When such a survey is embarked upon, all the recently discovered procedures for the testing of the blood fluids and the reaction of the white corpuscles will require to be pressed into service. And it will once and for all have to be realised that it is merely playing with the problem to try to guess from the temperature and aspect or survival of the patient what doses of vaccine should be given, how they should be interspaced, and what immunising effect is obtained.

(3) In the third category would be ranged an assortment of different diseases which have this in common: that there is in them a disregarded element

of bacterial infection. These are the class of cases spoken of above which are (so far as the combat with the bacterial infection is concerned), left, one may say, entirely without treatment. I shall take as my examples *pruritus ani*, *small-pox*, and *malignant disease*—making choice of these because these affections lie so far asunder in our thoughts that it is at first difficult to realise that there should be in them any common pathological factor.

Pruritus ani.—We have here a typical example of an infection which bears a label which leaves out of regard the element of bacterial infection. And the same holds of the text-book accounts. It will suffice to say that *pruritus ani* is the result of a bacterial infection of the skin—an infection in which streptococci appear to play the dominant rôle. In conformity with this is the fact that very good results are obtained by the inoculation of a streptococcus vaccine, or a mixed vaccine of streptococcus and staphylococcus.

Small-pox.—We have here the same triad of characters. The nomenclature does not suggest a bacterial infection. The text-book descriptions mention—but rather as a matter of curious and academic interest—that the staphylococcus and streptococcus may especially in severe cases come in as complications. And we have as our third feature the fact that no sort of provision is made for combating this element of bacterial infection.

Long ago I pointed out in connexion with the production of vaccine lymph from calves, that this could be obtained in much greater purity if the animal was preventively inoculated against the septic infection. And, at the same time, I suggested¹ that this same procedure might perhaps with advantage be resorted to both in vaccinating man and in the treatment of small-pox. Arising out of that suggestion I received in two

¹Wright, A. E.; and Knapp, H. H. G.: Causation and Treatment of Thrombosis Occurring in Connexion with Typhoid Fever, *Lancet* 2:1460, 1902. Wright, A. E.: Studies in Immunization and Their Application to the Diagnosis and Treatment of Bacterial Infections, London, A. Constable & Co., 1909.

private letters from medical men in Egypt and South America, respectively, accounts of dramatic successes obtained by inoculations of staphylococcus vaccine in small-pox. The cases ran a conspicuously milder course and all suppuration and scarring was avoided.

Malignant Disease.—We have here once more the same pathetic triad of characters. The label "malignant disease" places the disease in a pigeon hole of the doctor's mind which is quite remote from that occupied by bacterial infection. And again, the description in the text-books of pathology abstain in the interests of scientific purity from all mention of bacterial infection in cancer—except in so far as to bring for a moment a small artillery of contempt into action upon the notion that cancer is of bacterial origin. But cancer as a clinical entity is very largely a question of bacterial infection.

That is quite obviously so the moment that cancer makes its way through to the surface. It then very often becomes the seat of such a putrid mixed infection as is equalled only in neglected and sloughing war wounds.

But that is very far from being the whole of the picture. Comparatively early the new growth would seem to become the seat of a septic infection. That is an inference from the fact that cancer patients when tested by the op-

sonic method with staphylococci cultured from tumours (the so-called *Micrococcus neoformans* of Doyen) show very large divergencies from the normal. The fits of pain and the fluctuations of size in the tumour seem also referable to the ebb and flow of the inflammatory conditions in the tumour, and it is inflammatory infiltration which often renders the delimitation and enucleation of the tumour difficult. Again there is evidence which would seem to point to cancerous cachexia being due to the bacterial infection. Lastly—for it is impossible to mention all the points, streptococcal infection would appear to be responsible for that swelling of the arm so often seen after amputation of the breast—that swelling which finds, as we are told, a perfect explanation in the "mechanical blocking of the lymphatics."

Now the whole of this train of miseries is left untreated because the element of bacterial infection in malignant disease is put out of regard. It will suffice here to say that there is not one of these pathological effects which cannot be combated and alleviated by vaccine therapy. With this perhaps enough has been said to bring it home to the reader that beyond the confines of that territory which has already been occupied by vaccine therapy, there are wide expanses of country which are waiting to be explored.

